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EXAMINER	
SHEN, WU CHENG WINSTON	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,072	BROUGH, DOUGLAS E.	
	Examiner	Art Unit	
	WU-CHENG Winston SHEN	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07/24/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35,39-42,45-48 and 50-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,39-42,45-48 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/24/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim amendments filed on 07/24/2008 have been entered. Claims 1-34, 36-38, 43-44, and 49 are cancelled. Claims 35, 50, and 51 have been amended. Claims 35, 39-42, 45-48, and 50-53 are pending and currently under examination.

This application 10/586,072 is a 371 of PCT/US04/04891 filed on 02/19/2004, which is a Continuation-in-part of US application 10/373,249 filed on 02/24/2003, abandoned on 01/18/2007.

Claim Objection

1. Claim 35 is objected to because of the following informalities: **(i)** "*Hath1*" recited in claim 35 should read as "Hath1" without being italicized because in the art *Hath1* refers to the name of the gene *Hath1,* but the context of "Hath1" recited in claim 35 refers a protein; and **(ii)** it is advised that the limitation "a pharmaceutical composition comprising a subgroup A, B, D, E, or F adenoviral vector comprising a nucleic acid sequence ---" recited in claim 35 should read as "a pharmaceutical composition comprising an adenoviral vector selected from the group consisting of adenoviral vector A, B, D, E, and F subgroups, wherein the adenoviral vector comprises a nucleic acid sequence ---" for improved clarity of the claimed subject matter. Appropriate correction is required.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

2. Claims 35, 39-42, 45-48, and 50-53 **remain** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant's arguments filed 03/12/2007 have been fully considered and they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 3-4 of the office action mailed on 01/24/2008.

Amended claim 35 file don 07/24/2008 reads as following: A method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising a subgroup A, B, D, E, or F adenoviral vector comprising a nucleic acid sequence encoding Hath1 operably linked to a promoter that specifically functions in supporting cells of the inner ear wherein the nucleic acid sequence is expressed to produce Hath1 resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear.

(i) The aspect of the rejection pertaining to the limitation "(b) a chimeric coat protein ablated for binding to a native adenovirus receptor and comprising a non-native ligand, which non-native ligand enhances uptake of the adenoviral vector by cells of the inner ear" recited in claim 35 being unclear, is ***withdrawn*** because independent claim 35 has been amended and no longer recites this limitation.

(ii) With regard to the aspect of the rejection pertaining to claim 35 requiring the promoter "specifically" functions in supporting cells of the inner ear being unclear, this aspect of the rejection is ***maintained*** for the reasons of record advanced on page 4 of the office action mailed on 01/24/2008. It has been noted that the specification does not define the phrase "a

promoter that specifically functions in supporting cells of the inner ear". The metes and bounds of the phrase are unclear. Applicant's arguments filed 03/12/2007 have been fully considered and they are not persuasive because none of the reference submitted (Rio et al., *J. Comp., Neurol*, 442:156-162 (2002), Forge and Wright, *British Medical Bull*, 63:5-24 (2002), Zajic et al., *Hear. Res.*, 52(1): 59-71 (1991), Takumi et al., *Eur. J. Neurosci.*, 10(12): 3584-95 (1998), Lewis et al., *Mech. Dev.*, 78(1-2): 159-63 (1998), Lautermann et al., *Cell Tissue Res.*, 294(3): 415-20 (1998), Heller et al., *Proc. Natl. Acad. Sci. USA*, 95(19): 11400-5 (1998), Kwun et al., *Hear. Res.*, 183(1-2): 84-96 (2003), and Holt et al., *J. Neurophysiol.*, 81(4): 1881-8 (1999); see page 5 of Applicant's reply filed on 07/24/2008) provides a clear definition for the claimed limitation "a promoter that specifically functions in supporting cells of the inner ear". The information disclosed in these cited papers are directing to structures and functions of inner ear, and genes whose expression can be detected in the cells of inner ear. There is no disclosure from any of theses references that clearly states the promoters of these genes being "specifically functions in supporting cells of the inner ear", as recited in claim 35. Therefore, the metes and bounds of the limitation "a promoter that specifically functions in supporting cells of the inner ear" remain unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

3. Claims 35, 39-42, 45-48, and 50-53 **remain** rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.* 37 CFR 1.118 (a) states that "No amendment shall introduce **new matter** into the disclosure of an application after the filing date of the application".

(i) The aspect of the rejection pertaining to the limitation "a chimeric coat protein ablated for binding to a native adenovirus receptor" in the context of a non-Group C adenovirus vector" is ***withdrawn*** because the amended claims no longer recite this limitation.

(ii) The aspect of the rejection pertaining to the limitation "a promoter that specifically functions in supporting cells of the inner ear" is ***maintained*** for the reasons of record advanced on pages 4-9 of the office action mailed on 01/24/2008. It has been noted on page 8 of the office action mailed on 01/24/2008 that the specification does not define the term "specifically functions" in term of a promoter. Based on the commonly accepted scientific terminology, the term "a promoter that specifically functions ---" is interpreted as "the expression driven by the promoter is exclusive to ---". In this regard, the specification does not disclose any of disclosed promoters being specifically function in supporting cells of the inner ear. The relevant description is the statement "hes-1 promoter, which functions in supporting cells", however, there is no written description regarding the expression driven by hes-1 promoter being exclusive to the supporting cells of the inner ear, not any other cells or tissues.

(iii) New independent claims 35 recites the limitation "a pharmaceutical composition comprising *a subgroup A, B, D, E, or F adenoviral vector* comprising a nucleic acid sequence encoding *Hath1* operably linked to a promoter ---". *This aspect of the new matter rejection is necessitated by claim amendments filed by Applicant on 07/24/2008.* Applicant didn't indicate the support of this amended limitation in the reply filed on 07/24/2008. The specification discloses the presence of various subgroups (i.e. serotypes) of adenoviral vector (See paragraph [0025], US 2007/0141028, publication of instant application). However, there is no written description disclosed in the specification indicates that Applicant has contemplated expressing a *Hath1* gene from an adenoviral vector selected from the group consisting of adenoviral vector A, B, D, E, and F subgroups. It is worth noting that the AdMath1.11D construct described in Examples 2-4 is expressing Math1 (the mouse ortholog of human Hath1) from an adenoviral vector belonging to subgroup C, which is the known "first generation" of adenoviral vector that caused immune response in attempted gene therapy as described in the cited references, for instance, the reference by Brough et al., Activation of transgene expression by early region 4 is responsible for a high level of persistent transgene expression from adenovirus vectors in vivo, *J Virol.* 71(12):9206-13, 1997 (See paragraph [0089], US 2007/0141029, publication of instant application).

MPEP 2163.06 notes, "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an

invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, and a study of the entire application is often necessary to determine whether or not "new matter" is involved. *Applicant should therefore specifically point out the support for any amendments made to the disclosure.*

Enablement

4. Claims 35, 39-42, 45-48, and 50-53 **remain** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear a pharmaceutical composition comprising an adenoviral vector comprising a nucleic acid sequence encoding an atonal-associated factor Math1 (also known as Hath1 and Atoh1) operably linked to *a promoter that drives gene expression in supporting cells of the ear*, wherein the nucleic acid sequence is expressed to produce Math1 in supporting cells of the inner ear resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear, **does not** reasonably provide enablement for an adenoviral vector that expresses any atonal-associated factor other than *Math1 driven by a tissue specific promoter that drives expression specifically in the supporting cells of the inner ear.* Applicant's arguments filed 03/12/2007 have been fully considered and

they are not persuasive. Previous rejection is ***maintained*** for the reasons of record advanced on pages 9-13 of the office action mailed on 01/24/2008.

It is noted that the aspect of the rejection pertaining to any atonal-associated factor encompassed by claim 35 is withdrawn because claim 35 has been amended to recite Hath1. However, the claim amendments fail to address the basis of this scope of enablement hinged on the lack of enabling support on the limitation "a promoter that specifically functions in supporting cells of the inner cell", which remains required in amended claim 35.

Applicant's arguments

Applicant argues that claim 35 has been amended to recite an adenoviral vector comprising a nucleic acid sequence encoding Hath1. Thus, this aspect of the enablement rejection is rendered moot by the amendments to claim 35. Applicant argues that, the application discloses that the hes-1 promoter functions in supporting cells of the inner ear (see, e.g., paragraph 0055), and the prior art demonstrates that the *Hes1* gene is expressed in supporting cells of the inner ear and not in other cell types of the inner ear (see, e.g., Zheng et al., supra). Other genes that are expressed specifically in supporting cells of the mammalian inner ear also were known in the art at the time the present application was filed (see, e.g., Rio et al., *J. Comp., Neurol.*, 442:156-162 (2002), Forge and Wright, *British Medical Bull.*, 63:5-24 (2002), Zajic et al., *Hear. Res.,* 52(1): 59-71 (1991), Takumi et al., *Eur. J. Neurosci.*, 10(12): 3584-95 (1998), Lewis et al., *Mech. Dev.*, 78(1-2): 159-63 (1998), Lautermann et al., *Cell Tissue Res.*, 294(3): 415-20 (1998), Heller et al., *Proc. Natl. Acad. Sci. USA*, 95(19): 11400-5 (1998), Kwun et al.,

Hear. Res., 183(1-2): 84-96 (2003), and Holt et al., *J. Neurophysiol.*, 81(4): 1881-8 (1999)). Accordingly, using the guidance provided by the specification in combination with the knowledge in the art at the time the present application was filed, one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation.

Response to Applicant's arguments

The following discussions have been documented on pages 11-12 of the office action mailed on 07/24/2008.

With regard to promoter tissue specificity, the specification discloses that a tissue specific promoter for use in the inventive vector can be chosen by the ordinarily skilled artisan based upon the target tissue or cell-type. Suitable promoters include, but are not limited to, BRN.3C, BRN 3.1, the POU ORF3 factor promoter, BRK1, BRK3, the chordin promoter, the noggin promoter, the jagged1 promoter, the jagged2 promoter, and the notch promoter. However, it is noted that there is no disclosure in the specification that any of these promoter expresses exclusively in the supporting cells of inner ear, as recited in claim 35. The specification states that preferred tissue-specific promoters for use in the inventive method are specific to supporting cells or sensory hair cells, such as an atonal promoter or a myosin VIIa promoter, which function in hair cells, or a hes-1 promoter, which functions in supporting cells. Ideally, a promoter is selected that promotes transgene expression in scarred epithelium (See paragraph [0055], 2007/0141029, publication of instant application). In Example 2, the Math1 cDNA, which encodes a mouse atonal-associated factor, is operatively linked to the cytomegalovirus immediate early (CMV) promoter. It is noted that a CMV promoter is a strong

constitutive promoter that does not express a linked coding sequence in a tissue specific manner. Rather, the CMV promoter is a constitutive promoter that functions ubiquitously in all tissues, which includes supporting cells of the inner ear. *Claim 35 requires that the promoter 'specifically' functions in supporting cells of the inner ear. In this regard, the Examples 2-4 disclosed in the specification only indicates the Math 1 driven by CMV is expressed in the inner ear tissue, however, the Examples 2-4 do not demonstrate the Math1 driven by a CMV promoter being "specifically functions in support cells of inner ear", as recited in amended claim 35. The specification fails to provide any guidance with respect to what promoters are active specifically in supporting cells of the inner ear as claimed.*

In the art, the presence of tissue specific promoters that only express genes in a specific type of tissue has been well established. For instance, **Saukkonen et al.** teach various types of tissue specific promoters, including, for instance, hTERT (human telomerase reverse transcriptase) promoter being highly expressed only in tumor tissues, CEA (carcinoembryonic antigen) promoter being highly expressed in fetal tissue and being silent in adult tissue, and osteocalcin (OC) promoter being highly expressed only in bone tissues (See pages 686-687, section 4.2 Tissue-specific promoters, Saukkonen et al., Tissue-specific promoters for cancer gene therapy. *Expert Opin Biol Ther.* 4(5):683-96, 2004). *Given the art-accepted definition of "specific" with regard to promoter activity and the lack of any other defining features of "specific" in the specification, it appears the specification has failed to provide even a single promoter that functions specifically in the supporting cells of the inner ear such that one of skill in the art could carry out the claimed invention.*

Furthermore, based on the commonly accepted scientific terminology, the term "a promoter that specifically functions ---" is interpreted as "the expression driven by the promoter is exclusive to ---". In this regard, the specification does not provide any enabling support of any disclosed promoters being specifically function in supporting cells of the inner ear. The relevant description is the statement "hes-1 promoter, which functions in supporting cells", however, there is no enabling support regarding the expression driven by hes-1 promoter being exclusive to the supporting cells of the inner ear, not any other cells or tissues. Consistent with Examiner's conclusion based on disclosure in the specification, it worth noting that none of the reference submitted (Rio et al., *J. Comp., Neurol.*, 442:156-162 (2002), Forge and Wright, *British Medical Bull.*, 63:5-24 (2002), Zajic et al., *Hear. Res.*, 52(1): 59-71 (1991), Takumi et al., *Eur. J. Neurosci.*, 10(12): 3584-95 (1998), Lewis et al., *Mech. Dev.*, 78(1-2): 159-63 (1998), Lautermann et al., *Cell Tissue Res.*, 294(3): 415-20 (1998), Heller et al., *Proc. Natl. Acad. Sci. USA*, 95(19): 11400-5 (1998), Kwun et al., *Hear. Res.*, 183(1-2): 84-96 (2003), and Holt et al., *J. Neurophysiol.*, 81(4): 1881-8 (1999); see page 7 of Applicant's reply filed on 07/24/2008) provides enabling support for the claimed limitation "a promoter that specifically functions in supporting cells of the inner ear". The information disclosed in these cited papers are directed to those genes whose expression can be detected in the cells of inner ear (Heller et al., 1998, for instance), or directed to molecular architecture of inner ear (for instance, Forge et al., 2002). There is no disclosure from any of theses references that clearly demonstrate the promoters of any gene encoding those proteins detectable in inner ears being "specifically functions in supporting cells of the inner ear", as recited in claim 35. It is worth noting that the CMV promoter, as disclosed in Example 2 of specification as well as in cited reference Holt et al,

1991, is a strong constitutive promoter that functions ubiquitously in all tissues. Similarly, for instance, cited reference Heller et al., 1998 only disclosed presence of abundant collagen proteins in chicken inner ears; however, there is no disclosure in the reference regarding cloning of these collagen promoters and these promoter can drive the expression of any gene of interest, in instant case Hath1, in an inner ear specific manner as required by claim 35. In other words, there is no enabling support either in the specification or in the art for the presence and the use of an inner-ear specific promoter driving the expression of a coding sequence of interest (i.e. the coding sequences of Hath1 in instant case), as required by claim 35.

Therefore, in view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 35, 39-42, 45-48, and 50-53.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Previous rejection of claims 35-40, 43, 49-51, and 53 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al.,

(Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998), is ***withdrawn*** because the claims have been amended.

Neither Zoghbi et al. nor Roy et al. explicitly discloses adenoviral viral vectors of subgroup A, or B, or D, or E, or F.

6. Previous rejection of claims 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al. (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998) as applied to claims 35 and 40 above, and further in view of Kovesdi et al. (US patent 6,821,775, issue date, Nov. 23, 2004), is ***withdrawn*** because the claims have been amended.

None of Zoghbi et al., Roy et al., and Kovesdi et al. explicitly discloses adenoviral viral vectors of subgroup A, or B, or D, or E, or F.

7. Previous rejection of claims 45-48 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al. (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998) as applied to claim 35 above, and further in view of Staecker et al. (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. *Otolaryngol Head Neck Surg.* 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006), is ***withdrawn*** because the claims have been amended.

None of Zoghbi et al., Roy et al., and Staecker et al. explicitly discloses adenoviral viral vectors of subgroup A, or B, or D, or E, or F.

8. Previous rejection of claims 44 and 52 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Roy et al. (Roy et al., Circumvention of immunity to the adenovirus major coat protein hexon. *J Virol.* 72(8):6875-9, 1998) as applied to claims 35 and 43 above, and further in view of Kovesdi et al. (US patent 6,821,775, issue date, Nov. 23, 2004) and Wickham et al. (Wickham et al., US 6,455,314, issued 09/24/2002; This patent is listed as reference BM on the IDS filed by Applicant on 11/16/2006), is ***withdrawn*** because the claims have been amended.

None of Zoghbi et al., Roy et al., Kovesdi et al., and Wickham et al. explicitly discloses adenoviral viral vectors of subgroup A, or B, or D, or E, or F.

The following rejections under 35 U.S.C. 103(a) are necessitated by claim amendments filed on 07/24/2008.

9. Claims 35, 39, 40, 50, and 51under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006).

Zoghbi et al. disclose a method of generating hair cells for an animal comprising delivering directly to an inner ear of said animal an human atonal associated nucleic acid encoding the polypeptide HATH1 (SEQ ID NO: 58, 354 amino acid, columns 127-129) (see lines 25-33, col. 5, and claim 3), and HATH1 is a transcription factor belonging to the basic

helix-loop-helix (bHLH) family of proteins (See lines 30-32, col. 1). Zoghbi et al. also disclose such a method wherein the animal is a human, the atonal associated factor is MATH1, HATH1, the vector is a viral vector, an adenoviral vector, an adeno-associated viral vector, replication deficient (E1) adenoviral vector, and the hair cells are generated from adult differentiated cells of inner ear (see col.139, claims 1-8, and col. 47, lines 37-56, col. 48, example 16). Zoghbi et al. further disclose that different methods of delivery can be utilized to administer a vector into a cell. Examples include: (1) methods utilizing physical means, such as electroporation (electricity), a gene gun (physical force) or applying large volumes of a liquid (pressure); and (2) methods wherein said vector is complexed to another entity, such as a liposome, viral vector or transporter molecule (which binds to cell surface receptor, see col. 27, 2nd paragraph) (reading on claim 21 of instant application).

With regard to therapeutic effect by expressing Hath1 in treating hearing loss and balance disorder (claims 36-38 of instant application), Zoghbi et al. teach methods of treating an animal, including a human, for cerebellar granule neuron deficiencies, for generating hair cells, for treating hearing impairment or an imbalance disorder by administration of a vector expressing the atonal associated factor (MATH1 or HATH1) (See for instance, second paragraph, col. 5).

With regard to hes-1 promoter (claim 39 of instant application), Zoghbi et al. teaches that it is also possible, and often desirable, to use promoter or control sequences normally associated with the Math1 gene sequence, provided such control sequences are compatible with the host cell systems or the target cell (See Example 15). In this regard, Zoghbi et al. cites Zine et al., 2001, which taught that Hes1 and Math1 are expressed in the developing cochlea of inner ears

(Zine et al., Hes1 and Hes5 activities are required for the normal development of the hair cells in the mammalian inner ear, *The Journal of Neuroscience*, vol. 21, pp. 4712-4720, 2001).

However, Zoghbi et al. do not teach subgroup A, B, D, E, or F adenoviral vector.

Regarding subgroup A, B, D, E, or F adenoviral vector, **Falck-Pedersen et al.** specifically teaches the limitations on the use of group C adenoviral gene therapy vectors because a host can develop an immune response to the particular adenoviral vector being used in gene therapy as a result of natural exposure of the host to the same type of adenovirus prior to the initiation of gene therapy or as a result of the exposure of the host to the adenoviral vector in the course of the gene therapy itself (See lines 34-40 column 6, Falck-Pedersen et al.). Falck-Pedersen et al. characterized the oncogenic potential of adenoviral vectors of different subgroups (See Table, columns 1-2, Falck-Pedersen et al.), and examined the similarities and differences between various adenovirus groups by comparing the amino acid similarity and identity between the E1A and E1B gene products of Ad2 (group C), Ad5 (group C), Ad7 (group B), Ad12 (group A), and Ad40 (group F) adenoviruses (See Example 5, Falck-Pedersen et al.)

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector belonging to subgroup A, B, D, E, or F to circumvent host immunity taught by the teachings of Falck-Pedersen et al. because the presence of immune response to subgroup C adenovirus prevent efficacious adenovirus vector administration *in vivo*.

As such, the ordinary artisan would have been motivated to use the adenoviral vector belonging to subgroup A, B, D, E, or F to deliver nucleic acid sequence encoding Hath1 *in vivo*

because its effectiveness in expressing the gene of interest *in vivo* without provoking undesired host immunity to the adenoviral vector.

The level of skill in art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with an engineered coat protein in an adenoviral vector of subgroup A, B, D, E, or F, and deliver it to inner ear to generate sensory hair cells.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

10. Claims 41 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005), in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006) as applied to claims 35, 39, 40, 50, and 51above, and further in view of **Kovesdi et al.** (US patent 6,821,775, issue date, Nov. 23, 2004).

The teachings of Zoghbi et al. and Falck-Pedersen et al. are set forth in the rejection of claims 35, 39, 40, 50, and 51 under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005) in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, neither Zoghbi et al. nor Falck-Pedersen et al. teaches such a method wherein an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region.

Regarding an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region, Kovesdi et al. teach a replication deficient adenoviral vector with deletion of E1 and E4 and further comprise a pGUS spacer in the E4 region (see second paragraph, col. 7 and claim 1). Kovesdi et al. also disclose that said vector is used to deliver therapeutic effective amount of PEDF to eyes of mice to promote neovascularization. Kovesdi et al. further discloses that in the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector. However, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1).

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding Hath1 to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector of subgroup A, B, D, E, or F that circumvents host immunity taught by combined teachings of Falck-Pedersen et al. because the presence of immune response to the subgroup C adenoviral vector prevent efficacious adenovirus vector administration *in vivo*. Furthermore, It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings of Falck-Pedersen et al., and Kovesdi et al. in the method of generating hair cells to deliver atonal associated nucleic acid to inner ear of a subject taught by Zoghbi et al. because the vector taught by combined teachings of Falck-Pedersen et al. and Kovesdi et al. is able to (i) counteract the defect in growth of the E1/E4 deficient ADV and the defect in expression of the coat protein, and (ii) circumvent host immunity against adenoviral vector subgroup C.

As such, the ordinary artisan would have been motivated to use this vector to deliver atonal associated nucleic acid *in vivo* because of (i) its effectiveness in expressing a gene of interest *in vivo* without provoking host immunity to the adenoviral vector belonging to subgroup A, B, D, E, or F, and (ii) capability of expressing the engineered coat protein in the adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region since Kovesdi et al. discloses that in the absence of a spacer, production of fiber protein and/or viral growth of the multiply replication deficient adenoviral vector is reduced by comparison to that of a singly replication deficient adenoviral vector; however, inclusion of the spacer in at least one of the deficient adenoviral regions, preferably the E4 region, counteracts this defect in growth and fiber expression (See third paragraph, col. 6, and claim 1).

One of ordinary skill in the art would have reasonable expectation of success in delivering a nucleic acid sequence such encoding Hath1, to inner ear to generate sensory hair cells because the adenoviral vector of subgroup A, B, D, E, or F taught by combined teachings of Falck-Pedersen et al and Kovesdi et al can be used for proper expression of a exogenous gene such Hath1 due to the presence of deficiency in both E1 and E4 and the presence of a spacer in E4 region.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

11. Claims 45-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on

11/16/2006) as applied to claims 35, 39, 40, 50, and 51above, and further in view of **Staecker et al.** (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell loss. *Otolaryngol Head Neck Surg.* 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006).

The teachings of Zoghbi et al. and Falck-Pedersen et al. are set forth in the rejection of claims 35, 39, 40, 50, and 51under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, neither Zoghbi et al. nor Falck-Pedersen et al. teaches such a method wherein a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor Hath1.

Regarding a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor, Staecker et al. teach brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons (see abstract, bridging paragraph between left and right columns, page 10, and Figure 5).

It would have been obvious to one of ordinary skill in the art to combine the method of generating hair cells by delivering nucleic acid encoding an atonal associated factor Hath1 to the inner ear of a subject as taught by Zoghbi et al. using the adenoviral vector of subgroup A, B, D,

E or F that circumvents host immunity taught by Falck-Pedersen et al. because the presence of immune response to the subgroup C adenoviral vector prevents efficacious adenovirus vector administration *in vivo*. It would have been obvious to one of ordinary skill in the art to co-administer neurotrophic agent such as BDNF with atonal associated factor Hath1 in the method of changing sensory perception based on the combined teaching of Zoghbi et al., Falck-Pedersen et al., and Staecker et al.

One of ordinary skill in the art would have been motivated to include BDNF in the claimed method because BDNF has been shown by Staecker et al. to support the survival of auditory neurons. If the ordinary artisan intends to generate hair cells and improve hearing after hearing loss, the ordinary artisan would be motivated to preserve the auditory neurons which are vital for hearing.

The level of skill in the art is high. One of ordinary skill in the art would have reasonable expectation of success to co-administer the BDNF with atonal associated factor using a separate or the same vector in the method taught by Zoghbi et al. and Falck-Pedersen et al. because of the demonstration that a subgroup A, B, D, E, or F adenoviral vector can circumvent host immunity against subgroup C adenoviral vector by the combined teachings of Falck-Pedersen et al., and the demonstration that brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons by the teachings of Staecker et al.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

12. Claims 52 and 53 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Zoghbi et al.** (US patent 6,838,444, issued Jan. 4, 2005) in view of **Falck-Pedersen et al.** (US patent 5,837,511, issued Nov. 17, 1998; this reference is listed as reference #AJ in the IDS filed on 11/16/2006) as applied to claims 35, 39, 40, 50, and 51above, and further in view of **Wickham et al.** (Wickham et al., US 6,455,314, issued 09/24/2002; This patent is listed as reference BM on the IDS filed by Applicant on 11/16/2006) and **Mizuguchi et al.** (Mizuguchi et al., CAR- or αv integrin-binding ablated adenovirus vectors, but not fiber-modified vectors containing RGD peptide, do not change the systemic gene transfer properties in mice, *Gene Ther.* 9(12):769-76, 2002).

The teachings of Zoghbi et al. and Falck-Pedersen et al. are set forth in the rejection of claims 35, 39, 40, 50, and 51under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), in view of Falck-Pedersen et al. (US patent 5,837,511, issued Nov. 17, 1998).

However, neither Zoghbi et al. nor Falck-Pedersen et al. teaches an adenoviral vector mediated gene therapy with an alternatively targeted adenovirus.

Regarding an adenoviral vector with altered target cells (claims 52 and 53 of instant application), Wickham et al, teaches that coxsackievirus and adenovirus receptor (CAR) is the receptor for adenovirus serotype 2 and 5, citing (Bergelson et al., Science, 275, 1320-23 (1997) (See lines 35-40, col. 1), and mutations reducing affinity of adenovirus for the CAR protein (See Table 2 and Table 3). Mizuguchi et al. teaches that targeted gene delivery to the tissue of interest by recombinant adenovirus (Ad) vectors is limited by the relatively broad expression of the primary receptor, the coxsackievirus and adenovirus receptor (CAR), and the secondary receptor,

αv integrin; and this problem could be overcome by mutating the fiber and penton base, which bind with CAR and αv integrin, respectively.

It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by the combined teachings of Zoghbi et al. and Falck-Pedersen et al. in the method of generating hair cells to deliver nucleic acid encoding Hath1 to inner ear of a subject since the vector taught by combined teachings of Zoghbi et al. and Falck-Pedersen et al. that circumvents host immunity against adenoviral vector of subgroup C. It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by combined teachings of Falck-Pedersen et al., Wickham et al., and Mizuguchi et al. in the method of generating hair cells to deliver nucleic acid encoding Hath1 to inner ear of a subject taught by Zoghbi et al. because the vector taught by combined teachings of Falck-Pedersen et al., Wickham et al., and Mizuguchi et al. not only circumvents host immunity, but also successfully targets adenovirus to different cell types expressing different receptors of an adenoviral vector *in vivo*.

As such, the ordinary artisan would have been motivated to use the vector taught by combined teachings of Falck-Pedersen et al., Wickham et al., and Mizuguchi et al. to deliver nucleic acid encoding Hath1 *in vivo* because its effectiveness in expressing the gene of interest *in vivo* in desired target cell types, without provoking host immunity to the adenoviral vector of subgroup A, B, D, E, or F.

The level of skill in art of molecular cloning is high. One of ordinary skill in the art would have reasonable expectation of success to replace the native coat protein with altered coat protein, and deliver the adenoviral vector to desired target cells in inner ear to generate sensory hair cells because the adenoviral vector comprises engineered coat protein taught by combined

teachings of Falck-Pedersen et al., Wickham et al., and Mizuguchi et al. can be used to express therapeutic gene *Hath1* into cells of inner ear taught by Kovesdi et al., and the altered ligand-receptor interaction taught by Wickham et al. and Mizuguchi et al. can result in the adenoviral virus targeting to desired cells expressing different receptors of an adenoviral vector *in vivo* .

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

13. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the

currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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